AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

COMPLEMENTARY THERAPY ASSESSMENT
MARIJUANA IN THE TREATMENT OF GLAUCOMA

May 2003

SUMMARY

INTRODUCTION TO THE TOPIC

Marijuana is a mixture of the dried flowering leaves and tops from the plant *cannabis sativa*, and it contains over 400 chemicals. A medical use of marijuana has been to lower intraocular pressure (IOP) in patients with primary open-angle glaucoma (POAG).

CONCLUSIONS

Based on reviews by the National Eye Institute (NEI) and the Institute of Medicine and on available scientific evidence, the Task Force on Complementary Therapies believes that no scientific evidence has been found that demonstrates increased benefits and/or diminished risks of marijuana use to treat glaucoma compared with the wide variety of pharmaceutical agents now available.

BENEFITS

Initial studies in the 1970s reported that smoked marijuana resulted in lower IOP hours after administration. The NEI-sponsored studies demonstrated that some derivatives of marijuana did result in lowering of IOP when administered orally, intravenously, or by smoking, but not when topically applied to the eye. The duration of the pressure-lowering effect is reported to be in the range of 3 to 4 hours. Benefits also include euphoria as an acute effect.

RISKS

Potentially serious side effects associated with smoking marijuana include an increased heart rate and a decrease in blood pressure. Studies of single-administration marijuana use have shown a lowering of blood pressure concurrent with the lowering of IOP. This raises concerns that there may be compromised blood flow to the optic nerve, but no data have been published on the long-term systemic and ocular effects from the use of marijuana by patients with glaucoma.

Other adverse effects from the use of marijuana that have been reported include conjunctival hyperemia, impaired immune system response, impaired memory for recent events, difficulty concentrating, impaired motor coordination, tolerance to repeated doses, and short-term withdrawal symptoms after cessation. Smoking of marijuana also can lead to emphysema-like lung changes, increased risk of cancer, and poor pregnancy outcomes. Because duration of the induced fall in IOP is short, an individual would have to smoke a marijuana cigarette eight to ten times a day in order to control IOP over 24 hours.

REPORT

DESCRIPTION OF THE DRUG

Marijuana is a mixture of the dried flowering leaves and tops from the plant *cannabis sativa*, and it contains over 400 chemicals. The most prominent chemical group is called cannabinoids, and the main psychoactive cannabinoid is tetrahydrocannabinol (THC).

MECHANISM OF ACTION

The mechanism of action to lower IOP is not known. The route of administration can be oral, intravenous, topical, or inhaled by smoking, and it dictates many of the behavioral and physiologic consequences. Of these routes, smoking has the more rapid onset of psychoactive and other pharmacologic effects.

LEGAL STATUS

Marijuana is a Schedule I controlled substance, as defined in the Comprehensive Drug Abuse Prevention and Control Act of 1970.[1] The findings required for Schedule I are as follows: (A) high potential for abuse; (B) no currently accepted medical use in treatment in the U.S.; (C) lack of accepted safety for use under medical supervision. In November 1998, five states passed ballot initiatives to support medical marijuana. Except when authorized by law, it is illegal for any person to possess a controlled substance unless such substance was obtained directly by a valid prescription from a practitioner.

DEFINITION OF THE PROBLEM

Primary open-angle glaucoma (POAG) is a leading cause of blindness in the United States and the number one cause of blindness among African-Americans. It is estimated that 2.5 million Americans have POAG. POAG is a multifactorial disease characterized by an acquired loss of optic nerve fibers, and many patients with glaucoma have elevated pretreatment IOP. However, there is also significant individual variation in susceptibility of the optic nerve to elevated IOP.

SUMMARY OF EVIDENCE

The NEI sponsored research studies on the use of marijuana from 1978 to 1984. On February 18-19, 1997, the National Institutes of Health held the Workshop on the Medical Utility of Marijuana, providing a forum for expert speakers to address topics to a group of eight selected consultants known as the Expert Group. Speakers reviewed the literature on the potential efficacy of cannabinoids, including use in glaucoma. There was also a forum for the public to present their views and for discussion by the Expert Group. The Expert Group then prepared a report, focusing on the following four questions concerning specific uses of marijuana.

1. What research has been done and what is currently known about the possible medical uses of marijuana?
2. What are the major unanswered scientific questions?
3. What are the diseases or conditions for which marijuana might have potential as a treatment and that merit further study?

4. What special issues have to be considered in conducting clinical trials of the therapeutic uses of marijuana?

In 1999, the Institute of Medicine released a review of the scientific evidence to assess potential health benefits and risks of marijuana and its constituent cannabinoids.[2] Information for the study was gathered through scientific workshops, site visits to cannabis buyers' clubs and HIV/AIDS clinics, analysis of the relevant scientific literature, and by consultation with biomedical and social scientists. This was followed by public meetings that included presentations by experts.

To update this assessment, a search of the scientific literature in English was conducted in the MEDLINE and EMBASE databases and the Cochrane Library for the period 1999 to 2002. The search yielded 16 citations, of which one was relevant to this assessment. In a paper presented at the annual meeting of the American Ophthalmological Society, results of a case series (n=9) of patients unresponsive to glaucoma therapy who used either inhaled marijuana or orally administered delta-9-tetrahydrocannabinol capsules were presented.[3] Although an initial decrease in IOP was observed, this decrease was not sustained. Papers presented at this meeting are not subject to the peer review process.

BENEFITS

Initial studies in the 1970s reported that smoked marijuana resulted in lower IOP hours after administration.[4,5] The NEI-sponsored studies demonstrated that some derivatives of marijuana did result in lowering of IOP when administered orally, intravenously, or by smoking, but not when topically applied to the eye. The duration of the pressure-lowering effect is reported to be in the range of 3 to 4 hours.[6] Benefits also include euphoria as an acute effect. Also, earlier when fewer therapies were available for glaucoma, some patients might have had few acceptable or well-tolerated alternatives. There are no studies directly comparing the IOP-lowering effects of marijuana with currently available therapies.

RISKS:

Potentially serious side effects associated with smoking marijuana include an increased heart rate and a decrease in blood pressure. Studies of single-administration marijuana use have shown a lowering of blood pressure concurrent with the lowering of IOP.[7,8] This raises concerns that there may be compromised blood flow to the optic nerve, but no data have been published on the long-term systemic and ocular effects from the use of marijuana by patients with glaucoma.

Other adverse effects from the use of marijuana that have been reported include conjunctival hyperemia, impaired immune system response, impaired memory for recent events, difficulty concentrating, impaired motor coordination, tolerance to repeated doses, decreased testosterone in men who are chronic users, and short-term withdrawal symptoms after cessation.[9] Smoking of marijuana also can lead to emphysema-like lung changes,[10] increased risk of cancer, and poor pregnancy outcomes.[2] Because the duration of the induced fall in IOP is short, an individual would have to smoke a marijuana cigarette eight or ten times a day in order to control IOP over 24 hours.[10]

QUESTIONS FOR SCIENTIFIC INQUIRY

For future investigation, oral or topical cannabinoids might be a more promising avenue of study, given the side effects and psychotropic effects associated with smoking of marijuana. Specific questions for this might include the following:

- What is the mechanism of action for lowering of IOP by oral or topical cannabinoids?
- Do oral or topical cannabinoids lower IOP more safely and effectively than available pharmaceutical agents?
- Are oral or topical cannabinoids useful in lowering IOP when combined with pharmaceutical agents or with surgery?
- Are oral or topical cannabinoids useful in lowering IOP in patients who are not responsive or incompletely responsive to standard therapies?
- Do oral or topical cannabinoids safely and effectively prevent progressive optic nerve damage and consequent visual field loss?
- What are the long-term systemic and ocular side effects associated with the use of oral or topical cannabinoids by patients with glaucoma?

SUMMARY AND CONCLUSIONS

In a 1992 Information Statement entitled The Use of Marijuana in the Treatment of Glaucoma, the American Academy of Ophthalmology's Committee on Drugs concluded that there was no scientifically verifiable evidence that the use of marijuana is safe and effective in the treatment of glaucoma. The Academy could not support proposed legislation to transfer marijuana from Schedule I to Schedule II of the Controlled Substances Act in order to permit its use in treating glaucoma.[11] At the 1997 National Institutes of Health Workshop on the Medical Utility of Marijuana, the expert consultant concluded that "Marijuana is not generally accepted as a safe and effective treatment for glaucoma.... In glaucoma, there does not appear to be any obvious reason to use smoked marijuana as a stand-alone investigational therapy, as there are many available agents for treatment, and these topical preparations appear to be potentially ideal."[9]

In 1997, the NEI concluded that "none of these studies demonstrated that marijuana–or any of its components–could safely and effectively lower IOP any more than a variety of drugs then on the market.... Research to date has not investigated whether marijuana use offers any advantages over currently available glaucoma treatments or if it is useful when used in combination with standard therapies."[6] In 1998, an editorial in the *Archives of Ophthalmology* noted, "In summary, decreased blood pressure, decreased optic nerve blood flow and short duration of the IOP-lowering effect are significant actual and potential problems with marijuana, in addition to the psychotropic effects... To rationally determine marijuana's potential place in the antiglaucoma armamentarium, we should study cannabinoids as we would any other interesting class of compounds, rather than simply allowing or abandoning their use at present."[12]

The 1999 Institute of Medicine report concluded that although IOP can be reduced by using cannabinoids and marijuana, "... the effect is too short lived and requires too high doses, and there are too many side effects to recommend lifelong use in the treatment of glaucoma. The potential harmful effects of chronic marijuana smoking outweigh its modest benefits in the treatment of glaucoma. Clinical studies on the effects of smoked marijuana are unlikely to result

in improved treatment for glaucoma."[1] A principal investigator also concluded that "we did not find compelling evidence that marijuana should be used to treat glaucoma."[13]

In conclusion, the Academy Task Force on Complementary Therapies believes that based on a search of published peer-reviewed literature, no scientific evidence has been found that demonstrates increased benefits and/or diminished risks of marijuana use to treat glaucoma compared with the wide variety of pharmaceutical agents now available. These agents include topical miotics, beta adrenergic blockers, epinephrine derivatives, carbonic anhydrase inhibitors, alpha adrenergic agonists, and prostaglandin analogs as well as surgical treatments, such as laser trabeculoplasty, trabeculectomy, drainage devices, and cyclodestruction, which have been used effectively to lower IOP. If further investigation is desired, properly designed and analyzed studies are needed to describe the mechanism of action and to demonstrate the safety and effectiveness of oral and topical cannabinoids compared to other available therapies for treating glaucoma.

DEVELOPMENT OF COMPLEMENTARY THERAPY ASSESSMENTS

Complementary, or alternative therapies, are a growing part of health care in America. Americans spend an estimated $14 billion a year on alternative treatments. Most U.S. medical schools offer courses in alternative therapies. The editors of the *Journal of the American Medical Association* announced that publishing research on alternative therapies will be one of its priorities. More scrutiny and scientific objectivity is being applied to determine whether evidence supporting the effectiveness of complementary and alternative therapies exists.

The National Institutes of Health National Center for Complementary and Alternative Medicine has broadly defined complementary and alternative medicine as those treatments and health care practices that are not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies. The Cochrane Collaboration Complementary Medicine Field defines complementary medicine as including all such practices and ideas which are outside the domain of conventional medicine in several countries and defined by its users as preventing or treating illness, or promoting health and well being. These practices complement mainstream medicine by 1) contributing to a common whole; 2) satisfying a demand not met by conventional practices; and 3) diversifying the conceptual framework of medicine.[14]

In the fall of 1998, the Board of Trustees appointed a Task Force on Complementary Therapy to evaluate the peer-reviewed scientific literature on complementary therapies in eye care and develop an assessment on their safety and effectiveness in order to inform ophthalmologists and their patients. A scientifically grounded analysis of the data will help ophthalmologists and patients evaluate the research and thus make more rational decisions on appropriate treatment choices.

The Academy believes that complementary therapies should be evaluated similarly to traditional medicine: evidence of safety, efficacy, and effectiveness should be demonstrated.[16] Many therapies used in conventional medical practice also have not been as rigorously tested as they should be. Given the large numbers of patients affected and the health care expenditures involved, it is important that data and scientific information be used to base all treatment recommendations. In this way, we can encourage high-quality, rigorous research on complementary therapies.[16]

Ideally, a study of efficacy compares a treatment to a placebo or another treatment, using a double-masked controlled trial and well-defined protocol. Reports should describe enrollment procedures, eligibility criteria, clinical characteristics of the patients, methods for diagnosis, randomization method, definition of treatment, control conditions, and length of treatment. They should also use standardized outcomes and appropriate statistical analyses.

The goal of these assessments is to provide objective information about complementary therapies and to provide a scientific basis for physicians to advise their patients, when asked.

To accomplish these goals, the assessments, in general, are intended to do the following:

- Describe the scientific rationale or mechanism for action for the complementary therapy.
- Describe the methods and basis for collecting evidence.
- Describe the relevant evidence.
- Summarize the benefits and risks of the complementary therapy.
- Pose questions for future research inquiry.
- Summarize the evidence on safety and effectiveness.

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Approved by the Quality of Care Secretariat June 1999
Revised April 2003 and approved by the Quality of Care Secretariat May 2003